ORIGINAL ARTICLE

COMPARISON OF BONE MINERAL DENSITY BETWEEN TYPE 2 DIABETIC AND NON-DIABETIC PATIENTS AND ITS CORRELATION WITH SERUM INSULIN, HbA1c AND DURATION OF ILLNESS IN TYPE 2 DIABETIC PATIENTS

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Background: Relationship between osteoporosis and type II diabetes mellitus (T2DM) is complex. Although many studies have been conducted, still it remains a controversial subject. Osteoporosis is diagnosed by measuring bone mineral density and the current gold standard is quantitative computed tomography (QCT). This study aimed to compare the bone mineral density (BMD) in type 2 diabetics and non-diabetics using QCT, and to correlate BMD with duration of disease, Glycated Haemoglobin A (HbA1c) level, and Serum Insulin level. **Methods:** This cross-sectional study was conducted between Aug 2016 and Dec 2019 at Radiology Department, Mayo Hospital Lahore. One hundred type 2 DM and 100 healthy individuals were included. BMD, HbA1c, Fasting Blood Sugar and serum insulin levels were measured in all. BMD, HbA1c and Serum Insulin were compared between the cases and controls. Moreover, the correlation between bone mineral densities, duration of disease, HbA1c and serum Insulin level was assessed. **Results:** A significant difference between HbA1c, fasting blood sugar levels and serum insulin levels of the two groups was noted. However, no significant difference was observed in the QCT scoring of the groups. Osteoporosis was diagnosed in 19 diabetics and 12 healthy individuals. BMD changes significantly correlated with the duration of illness and HbA1c. There was no significant correlation and between BMD and Serum Insulin Levels. **Conclusion:** BMD shows a significant correlation with duration of diabetes and HbA1c. These factors play a negative impact on BMD in T2DM. There was no significant correlation between serum insulin and BMD.

Keywords: Bone density, osteoporosis, T2DM, glycated haemoglobin A, HbA1c, Insulin, QCT

Pak J Physiol 2021;17(1):41–5

INTRODUCTION

Diabetes Mellitus (DM) is the most common metabolic disorder of the bone with 11.77% prevalence in Pakistan. It is considered an independent risk factor for fractures which is not related to increase BMI or classical osteoporosis risk factors.[1] Nearly 60% of patients with Typ2 2 Diabetes Mellitus (T2DM) have low Bone Mineral Density (BMD).[2]

There are multiple mechanisms through which bone is affected in type 2 diabetics which include insulin deficiency or resistance, hyperglycaemia and atherosclerosis. However, the exact mechanism is still unknown.[3] Diabetes is a chronic metabolic disorder which can cause damage to various organ system. A complex pathophysiological interaction exists between T2DM and bone health. T2DM directly affects bone metabolism and strength, and the indirect effect of anti-diabetic medicine induced altered bone metabolism is also observed.[4] Quite a lot of evidence shows that increased blood sugar levels cause impairment in bone matrix and biochemical formulation.[5]

Assessment of osteoporosis is done by the measurement of BMD which is heritable and varies according to race, age and sex.[6] There are different method of measuring the bone mineral density, however, most commonly used is dual-energy X-ray absorptiometry (DXA) and This study aimed to compare the BMD, HbA1c and serum insulin between type 2 diabetic and non-diabetic patients of same age group and to correlate the BMD using quantitative computed tomography (QCT) with the duration of disease, HbA1c levels, serum insulin levels in the diabetic group. (QCT).[7] DXA due to its low radiation dose and cost is most commonly used.[8] However, QCT provides a similar and more sensitive method for detecting bone mineral loss when compared to DXA.[9]

The main advantage of the QCT over DXA is the ability to separate the mineral density of trabecular and cortical bone.[10] As trabecular bone is metabolically more active than cortical bone, the changes in trabecular bone are considered to be the most sensitive predictor of early bone loss and vertebral fracture risk.[11] QCT provides the true volumetric density of trabecular bone separately from the cortical bone in units of g/Cm^3 whereas DXA estimates areal density measured in g/Cm^2.[12] There are errors due to spinal degenerative changes and aortic calcification in DXA value. QCT is

independent of BMI whereas increase BMI causes DXA BMD values to be high.[13]

This study aimed to compare the BMD, HbA1c and serum insulin between type 2 diabetic and non-diabetic patients of same age group and to correlate the BMD using quantitative computed tomography (QCT) with the duration of disease, HbA1c levels, serum insulin levels in the diabetic group.

MATERIAL AND METHODS

It was an analytic, cross-sectional study, conducted at Department of Diagnostic Radiology and Medical Imaging, Mayo Hospital Lahore, from 22nd August 2016 to 30th December 2019. The study was approved by the Advance Board of Research and Studies at King Edward Medical University and written informed consent was taken from all participants. The sample size was estimated using the formula:

$$n = \frac{z^2_{1-\frac{\alpha}{2}}(2\sigma^2)}{d^2}$$

With 95% confidence interval, 10% margin of error, and expected prevalence of osteoporosis in diabetes mellitus being 60%, the calculated sample size was 57, but 100 subjects were taken in each group. According to the inclusion and exclusion criteria, 100 diagnosed cases of T2DM aged 40–60 years and 100 healthy controls were selected.[14] The minimum duration of insulin therapy for the subjects was one year. Both groups were matched for age and gender. Non-probability purposive sampling technique was used for data collection. Diabetic patients who were on oral hypoglycaemics, suffering from any other endocrine abnormality, immobilized for more than three weeks due to any trauma, fracture or fixation by plaster or quiet rest in bed due to any illness (e.g., prolonged tuberculosis or paralysis), had a disease affecting bone metabolism (e.g., rickets, osteomalacia, osteogenesis imperfecta, fibrous dysplasia), past medication affecting bone (e.g., steroids, cyclosporine, anti-seizure drugs, depo provera, anti-cancer drugs, antihypertensives etc.) were excluded from the study.

A detailed clinical history was taken from a total of 200 individuals fulfilling the criteria regarding previous prolonged illness, metabolic and endocrine disease. HbA1c and serum insulin levels were estimated using CERA STAT 1000 and Siemens Immulite-2000. Fasting blood sugar was estimated with Accu-Chek® glucometer. Both groups underwent QCT for measurement of BMD on CT Scanner (Toshiba Xvision EX). Lateral scout image of the patient's lumbar spine was obtained including the first three lumbar vertebrae.[15] Three separate slices with a thickness of 10 mm were selected. After obtaining the necessary axial slices, selection of a region of interest (ROI) was selected inside the cancellous part of the vertebral body, not including the cortical bone. Fractured vertebrae and vertebrae with obvious pathology like deformity, haemangioma and metastasis were excluded. The CT density of ROI (Figure-1) was estimated by the software automatically and plotted onto the regression line. Using the regression line, BMD of the selected ROI was calculated by the software and was shown in units of mg/Cm^3. The procedure was repeated for each of the three vertebral slices obtained and the software took out an average BMD value obtained from the three slices. Using Felsenberg classification recommended by the American College of Radiology, BMD values were classified into osteoporosis, osteopenia and normal.[16]

Data analysis was carried out through SPSS-20. The Spearman correlation coefficient was applied to see the correlation and interdependency of BMD, duration of diabetes (Only for cases), while HbA1c level and serum insulin level in cases and controls. Shapiro Wilk test was used to confirm the normality of data. Based on distribution of data, Mann Whitney U test was applied to compare the BMD, HbA1c and serum insulin levels, and $p<0.05$ was taken as significant.

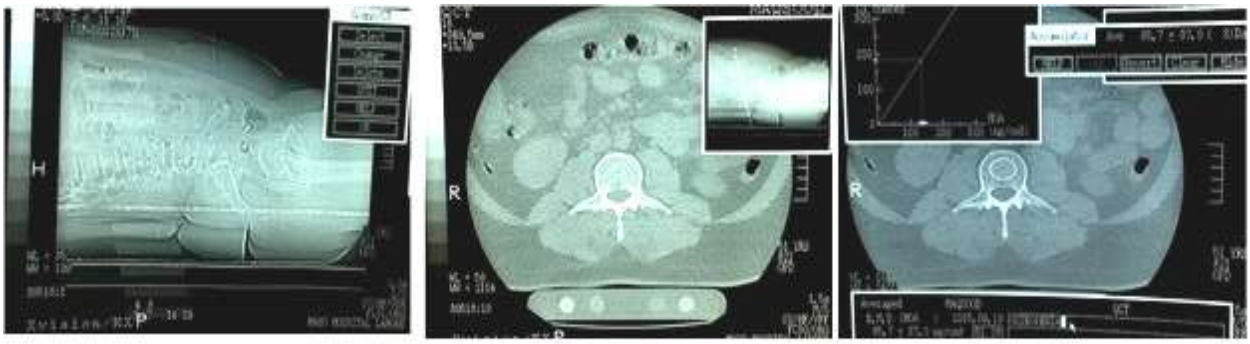

Figure-1: QCT in 56 years old diabetic female done on Toshiba Xvision/EX. (a) scanogram (b) ROI taken along with the level of vertebrae taken and position of the phantom (c) the BMD taken from 3 vertebrae is shown as Averaged BMD

RESULTS

The study included 100 subjects suffering from T2DM and 100 healthy controls. There were 57% males and 43% females in the group with T2DM. Control group included 52% males and 48% females. No significant difference was observed between the ages of the two groups (p=0.771). The duration of diabetes among cases was 6.15±2.92 ranged from 2 to 14 years. (Table-1).

There was a significant difference between height, BMI, HbA1c, fasting blood sugar and serum insulin levels of the 2 groups with p-values of 0.024, 0.001, 0.001, 0.001, and 0.001 respectively. However, no significant difference was noted in the weight and QCT scoring of the two groups (p=0.430, p=0.477).

Among cases QCT findings showed that osteoporosis was diagnosed in 19 cases, osteopenia in 67 cases and 14 cases were normal. While in controls QCT findings showed that osteoporosis was diagnosed in 12 controls, osteopenia in 79 and 9 controls had normal findings on QCT.

The correlation of BMD with the duration of diabetes in cases is illustrated in Figure-2, Table-2. Correlation of BMD with HbA1c and serum insulin level in cases and controls is shown in Figure-3 and 4.

Table-1: Comparison of study parameters between cases and controls

Parameter		Mean±SD	Median (IQR)	p
Age (years)	Cases	48.26±6.16	48.0 (9.00)	0.771
	Controls	48.12±4.97	48.0 (6.00)	
BMD	Cases	98.09±17.61	100.0 (23.75)	0.477
	Controls	99.8±15.39	102.0 (21.50)	
HbA1c	Cases	9.75±1.27	9.8 (1.00)	0.001*
	Controls	6.37±0.41	6.4 (0.70)	
Serum insulin	Cases	27.91±8.10	27.0 (5.00)	0.001*
	Controls	20.25±2.59	21.0 (3.00)	
Duration of illness	Cases	6.15±2.92	6.0 (4.00)	

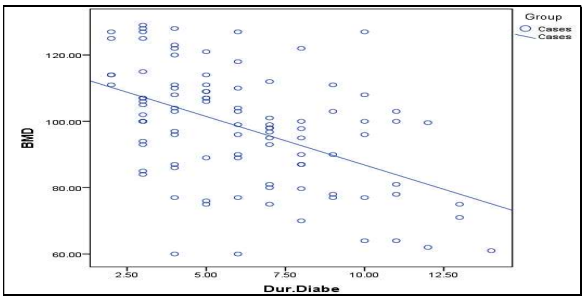

Figure-2: Correlation of BMD with duration of diabetes in cases

Spearman correlation test: Correlations Coefficient= -0.470, p= 0.001

Table-2: Correlation between study parameters in cases and controls

	Type 2 diabetics			Healthy controls	
BMD	**HbA1c**	**Serum insulin**	**Duration**	**HbA1c**	**Serum insulin**
r	0.360	0.158	0.47	0.112	0.353
p	0.001	0.116	0.001	0.228	0.001

All values generated by Spearman correlation test

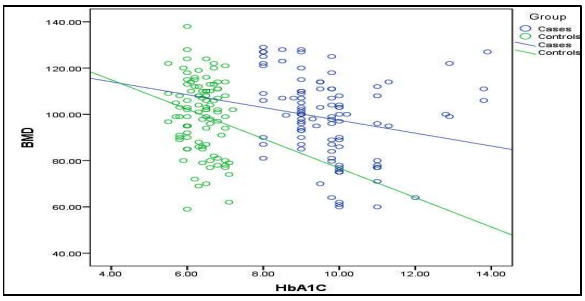

Figure-3: Correlation of BMD with HbA1c in cases and controls

Cases: Type 2 Diabetic Patients, **Controls:** Non-diabetic
Correlations Coefficient: Cases= -0.360, p=0.001, **Controls=** -0.112, p=0.228

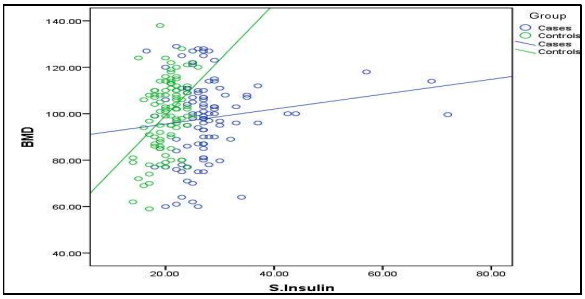

Figure-4: Correlation of BMD with serum insulin level in cases and controls (Spearman correlation)

Cases: Type 2 Diabetic Patients, **Controls:** Non-diabetic
Correlations Coefficient: Cases= -0.158, p=0.116, **Controls=** -0.353, p=0.001

DISCUSSION

Osteoporosis and diabetes are currently the most widely discussed diseases and are believed to be inter-related that is why they are often found to be present simultaneously. However, there is quite a lot of evidence which shows that increased blood sugar level causes impairment in bone matrix and biochemical formulation. Reduced biomechanical competency is often found even when there is normal or increased BMD as evaluated by DXA Scanner13 The current gold standard for the measurement of bone structure is high resolution peripheral quantitative CT (HRQCT). Unfortunately, in the clinical arena, this is limited by radiation exposure and the cost of investigation. Therefore, it is relatively rarely used.[16]

In this study, QCT findings showed that 19 patients had osteoporosis whereas among controls only 12 individuals had osteoporosis. However, 79 controls and 67 cases were diagnosed with osteopenia. QCT findings were normal among 14 cases and among controls normal findings were seen in only 9 participants. There was no significant difference between the BMD of two groups among cases and controls.

The randomized prospective controlled single-blinded study conducted in Turkey included type 2 diabetics in the patient group and healthy individuals

were included in the control group. The bone mineral densities of the cases were found to be significantly low in terms of the lumbar (L1–4) T scores in the type 2 diabetes group. However, there was no significant difference found between the BMD of type 2 diabetics and healthy controls.[17] In line with our study results, a study showed that the type 2 diabetics with low BMD values were observed to have long-term diabetes and menopause, to have poor glucose control, and to have disordered renal functions.[18]

A study conducted by Sosa et al. showed no significant difference in terms of BMD estimated through DEXA and QCT.[19] Studies suggest that type 2 DM patients, individuals using dietary and oral antidiabetic, and individuals taking insulin have lower BMD values.[20]

Many mechanisms have been asserted to contribute to diabetic osteopenia. One of them is that it can lead to diabetic osteopenia due to deficiency in anabolic activation of insulin.[20] Another mechanism noted in diabetic osteopenia is the suppression of osteoblastic bone formation.[21]

Rotterdam study suggests that individuals with type 2 diabetes have increased fracture risk despite higher BMD. Contrary to our study results, diabetic patients had a slightly higher BMD than the non-diabetic group. Poor glycaemic control in type 2 diabetes was associated with fracture risk, high BMD, and thicker femoral cortices in narrower bones. It is proposed that fragility in apparently 'strong' bones among patients with poorly controlled diabetes is due to altered bone repair process resulting in porous cortices and microfractures.[22]

Contrary to our study, a study conducted by Bridges and colleagues showed no significant correlation between HbA1c and BMD in diabetics.[23] A weak negative correlation is found between HbA1c and BMD in the study conducted on south Indian diabetic patients.[24]

A study conducted on East Asian men showed that patients with DM for >5 years had lower mean BMD in the total hip and femoral neck than those with DM for ≤5 years.[25]

CONCLUSION

Type II diabetes mellitus has an impact on BMD and it increases the risk of fracture. Negative effects of the disease are dependent upon the duration of disease and degree of glycaemic control. Insulin resistance in T2DM deteriorates osteoblast proliferation and activity but enhances osteoclast activity, leading to uncoupled bone remodelling. Frequency of osteoporosis was low while osteopenia was high in type 2 diabetic patients. BMD showed a significant correlation for the duration of diabetes and HbA1c hence these factors play a negative impact on bone mineral density in type 2 diabetic patients. However, no significant effect of serum insulin level on BMD was noted. By improving the glycaemic control damage or loss of BMD can be prevented.

Inability to measure bone turnover markers is surely a limitation to explain different correlation findings in both groups. HbA1c level measured at the time when measurements of BMD reflected only short-term glycaemic control. It is purposed to investigate and correlate bone markers, serial HbA1c levels, and BMD simultaneously in future studies.

REFERENCES

1. Meo SA, Zia I, Bukhari IA, Arain SA. Type 2 diabetes mellitus in Pakistan: Current prevalence and future forecast. J Pak Medical Assoc 2016;66(12):1637–42.
2. Wang B, Yang XN. Relationship between DEXA bone mineral density measurement results and serum cytokines as well as insulin resistance in patients with type 2 diabetes mellitus and osteoporosis. J Hainan Med Univ 2017;23(2):151–5.
3. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol 2017;13(4):208–19.
4. Sanches CP, Vianna AG, de Carvalho Barreto F. The impact of type 2 diabetes on bone metabolism. Diabetol Metab Syndr 2017;9:85.
5. Costantini S, Conte C. Bone health in diabetes and prediabetes. World J Diabetes 2019;10(8):421–45.
6. Link TM, Kazakia G. Update on Imaging-Based Measurement of Bone Mineral Density and Quality. Curr Rheumatol Rep 2020;22(5):13.
7. Damilakis J, Adams JE, Guglielmi G, Link TM. Radiation exposure in X-ray-based imaging techniques used in osteoporosis. Eur Radiol 2010;20(11):2707–14.
8. Link TM. Osteoporosis imaging: state of the art and advanced imaging. Radiology 2012;263(1):3–17.
9. Mao SS, Li D, Syed YS, Gao Y, Luo Y, Flores F, *et al*. Thoracic quantitative computed tomography (QCT) can sensitively monitor bone mineral metabolism: comparison of thoracic QCT vs lumbar QCT and dual-energy X-ray absorptiometry in detection of age-relative change in bone mineral density. Acad Radiol 2017;24(12):1582–7.
10. Oei L, Koromani F, Rivadeneira F, Zillikens MC, Oei EH. Quantitative imaging methods in osteoporosis. Quant Imaging Med Surg 2016;6(6):680–98.
11. Ziemlewicz TJ, Maciejewski A, Binkley N, Brett AD, Brown JK, Pickhardt PJ. Opportunistic quantitative CT bone mineral density measurement at the proximal femur using routine contrast-enhanced scans: direct comparison with DXA in 355 adults. J Bone Miner Res 2016;31(10):1835–40.
12. Yu EW, Thomas BJ, Brown JK, Finkelstein JS. Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. J Bone Miner Res 2012;27(1):119–24.
13. Vestergaard P. Diabetes and osteoporosis—cause for concern?. Front Endocrinol (Lausanne) 2014;5:53.
14. Shan PF, Wu XP, Zhang H, Cao XZ, Yuan LQ, Liao EY. Age-related bone mineral density, osteoporosis rate and risk of vertebral fracture in mainland Chinese women with type 2 diabetes mellitus. J Endocrinol Invest 2011;34(3):190–6.
15. Ma XH, Zhang W, Wang Y, Xue P, Li YK. Comparison of the spine and hip BMD assessments derived from quantitative computed tomography. Int J Endocrinol 2015;2015:675340.
16. Antonopoulou M, Bahtiyar G, Banerji MA, Sacerdote AS. Diabetes and bone health. Maturitas. 2013;76(3):253–9.
17. Adil C, Aydın T, Taşpınar Ö, Kızıltan H, Eriş AH, Hocaoglu IT, *et al*. Bone mineral density evaluation of patients with type 2 diabetes mellitus. J Phys Ther Sci 2015;27(1):179–82.

18. Kao CH, Tsou CT, Chen CC, Wang SJ. Bone mineral density in patients with noninsulin-dependent diabetes mellitus by dual photon absorptiometry. Nucl Med Commun 1993;14(5):373–7.
19. Sosa M, Dominguez M, Navarro MC, Segarra MC, Hernandez D, de Pablos P, *et al*. Bone mineral metabolism is normal in non-insulin-dependent diabetes mellitus. J Diabetes Complications 1996;10(4):201–5.
20. Kocián J, Brunová J. Diabetic osteopathy. 4. Laboratory findings. Vnitr Lek 1990;36(5):460–6.
21. Takizawa M, Kameyama K, Maruyama M, Ishida H. Bone loss in type 2 diabetes mellitus–diabetic osteopenia. Nihon Rinsho 2003;61(2):287–91. [Article in Japanese]
22. Oei L, Zillikens MC, Dehghan A, Buitendijk GH, Castaño-Betancourt MC, Estrada K, *et al*. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. Diabetes Care 2013;36(6):1619–28.
23. Bridges MJ, Moochhala SH, Barbour J, Kelly CA. Influence of diabetes on peripheral bone mineral density in men: a controlled study. Acta Diabetol 2005;42(2):82–6.
24. Mathen PG, Thabah MM, Zachariah B, Das AK. Decreased bone mineral density at the femoral neck and lumbar spine in South Indian patients with type 2 diabetes. J Clin Diagn Res JCDR 2015;9(9):OC08–12.
25. Jang M, Kim H, Lea S, Oh S, Kim JS, Oh B. Effect of duration of diabetes on bone mineral density: a population study on East Asian males. BMC Endocr Disord 2018;18(1):61.

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Received: 8 Jan 2021 **Reviewed: 2 Mar 2021** **Accepted: 7 Mar 2021**

Authors' Contribution

SMD: Conception of idea, design, methodology, data acquisition, interpretation and data analysis, and literature review.
BR: methodology, data acquisition, interpretation and data analysis, and literature review.
SR: Review of intellectual contents, study design and ethical issues.
AHAR: Data analysis, work draft, literature review and bibliography.
FM: Methodology, inclusion exclusion criteria.

Conflict of Interest: None to declare
Funding: None to declare